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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 06/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/085,783	LIEW ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2004 and 09 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35 and 45-73* is/are pending in the application.

4a) Of the above claim(s) *1-35 and 45-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-73* is/are rejected.

7)☒ Claim(s) *58-73* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 October 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/02;2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner handling this application has changed. Please address all future correspondence to Juliet Switzer, Art Unit 1634.

Election/Restrictions

2. Applicant's election of the methods of claims 58-73, drawn to methods of diagnosing osteoarthritis in an individual is acknowledged. Pending claims 1-35 and 45-57 are WITHDRAWN from prosecution.

3. Insofar as the traversal set forth in the response received 10/7/04 is relevant to the instantly examined claims the traversal is addressed. In the traversal applicants argue that the elected methods are related to the products of group XV (drawn to microarrays and kits comprising microarrays) as product and product by process. However, this is not persuasive because the claims are related as product and process for use as stated in the restriction requirement mailed 7/9/04, see page 5 therein. The products of group XV can be used in a variety of methods (as exemplified by the claims in the instant invention), and as discussed in the restriction requirement. Thus, the traversal is not persuasive.

4. The newly added claims 58-73 recite methods which require determining expression levels of "two or more" or "three or more" transcripts which correspond to genes selected from Figure 6. Thus, the claims read on a multitude of different methods, each of which is separate and distinct one from another because they require the assay of different possible groups of genes within the claimed methods (i.e. every possible group of "two or more" of the over 5,000 genes listed in Figure 6). The search and examination of all possible groups would pose an enormous burden on the examiner and on the PTO search resources. These claims are subject to

further restriction requirement wherein a single group or "two or more" or "three or more" is elected for prosecution. Prosecution will be limited to the examination of the elected group. If methods which utilize the elected group are found to be allowable, all groups which recite those groups will be rejoined.

5. In a telephone conversation with Amy DeCloux on 5/16/05 the election of a single group of ten genes from Figure 6 was made. The elected group was identified by their line gene name and line number from Figure 6 and includes beta-2 microblobulin gene (line 6), MAFB/Kreisler basic region/leucine zipper trans (line 316), laminin gamma 1 (line 988), Krueppel-related binding protein (PF4) (line 1304), interleukin 13 receptor alpha1 (line 1366), B-Cell CLL/lymphoma 6 (zinc finger protein 51 (line 2287), tumor necrosis factor alpha-induced protein 6 (line 2654), PER1 gene (=Rigui (RIGUI)) (line 3596), zinc finger RNA binding protein (Zfr) (line 4595), cyclin C (CCNC) (line 5670).

6. The previous election of two genes (in the paper received 3/9/05).

Claim Objections

7. The claims are objected to because they refer to the Figures. MPEP 2173(s) states "Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience."

Specification

8. It is suggested that the figures which contain text concerning the differential expression of genes in OA be incorporated as TABLES into the specification. As figures, this data is not text searchable in US patent databases. Putting the information into text-based tables would make the information more search accessible to the public in the event that this applicant issues as a patent.

Drawings

9. Applicant removed figures 14 and 14A from the newly filed set of drawings provided 10/12/02 (These drawings provided sequences which now appear in the sequence listing, so the removal of the drawings is permissible). However, Applicant did not renumber the remaining drawings, and so now the remaining drawings are not numbered consecutively in order. Applicant must submit new drawings that are all numbered in proper order, without skipping a number. Applicant is advised that the specification should also be amended to reflect the new numbering. Further, applicant should remove reference to figures 14 and 14A from the brief description of the drawings since these have been removed from the drawings.

Compact Disc Submission

10. The amendment filed 5/30/03 amends or adds a compact disc(s). See 37 CFR 1.77(b)(4) and 1.52(e)(5). Applicant is required to update or insert an incorporation-by-reference of the material on the compact disc(s) in the specification. An incorporation by reference was filed with a previously submitted compact disk (10/21/02) but this compact disk was defective. Further the incorporation-by-reference was defective because it did not list the date that the files on the disk were created.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 58-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite over the language "RNA transcripts which correspond to" because it is not clear what it means for an RNA transcript to correspond to a gene. The specification does not define the term, and it is unclear if the term is meant to encompass only the expression of the human gene recited in the Figure or if the term is also meant to encompass the expression of genes that are similar to the human gene in other animals and also in humans, etc. The claims are further indefinite because it is not clear what is meant by the genes "selected from Figure 6." Figure 6 refers to genes by gene name and then provides an accession number. It is not clear, therefore, if the claims intend to be requiring the assay of expression of the sequence that is in the accession number (whose source and sequence are undefined in the specification) or if the claims intend to require the assay of any gene which has the name recited in the "Gene Name" column of the figure, including any potential variants or alternate splices of the gene. From the teachings in the Figure and the description of the figure, it is entirely unclear what sequence is being referred to in the "Accession #" column since there is no guidance given as to what database is being referred to by accession number. The claims should be clarified as to what precisely is to be determined.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 58-73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Invention

Each of the rejected claims is drawn to a method for diagnosing osteoarthritis, mild osteoarthritis, moderate osteoarthritis, marked osteoarthritis, or severe osteoarthritis. The claims all recite a method step of "determining the level" of "RNA transcripts corresponding to...genes...selected from Figure 6 in a sample from an individual suspected of having or being afflicted with" the particular level of OA recited in the claims. The elected invention requires the determining of the level of ten genes in particular that were selected from Figure 6. Thus, the nature of the claimed invention requires the knowledge of an association between the gene expression of the ten elected genes and osteoarthritis, or some stage of osteoarthritis as recited in the claims. The practice of the claimed invention for the "diagnosis" of OA or the staging of OA requires the knowledge that not only are genes differentially expressed in OA, but also that this expression is specific to OA or a stage of OA in such a way that one can reliably draw conclusions for the diagnosis of OA based on the gene expression patterns.

Scope of the invention

The rejected claims include claims for diagnosing all OA, and also for diagnosing different stages of OA. The claims recite "determining the level" of RNA transcripts "in a

sample" and are sufficiently broad so as to include the assay of any sample in an individual, including samples of blood, synovial fluid, and cartilage, for example, each of which are specifically recited in claims 70-72. The language used to define the detected transcripts is also broad in nature, requiring only that the level of transcripts "corresponding" to genes recited in Figure 6 be determined- and thus encompasses the determination of gene expression for genes which are homologues, variants, and the like of the recited genes. As noted in the 112 2nd rejections, these claims are unclear as to the precise nature of the claimed invention, and this lack of clarity must reasonably be interpreted broadly with regard to what sequences are to be detected within the instant claims. Further, the claims are sufficiently broad so as to include the diagnosis of OA in a patient of any species that would have a transcripts that hybridize or "correspond" to the transcripts listed in Figure 6.

Guidance in the specification and Working examples

The specification teaches that "'diagnosis' refers to a process of determining if an individual is afflicted with a disease or ailment (p. 19, lines 9-10)." The specification does not provide a single working example where the claimed method is actually practiced for the diagnosis or staging of OA in a patient, human or otherwise. The specification provides an experimental section with "examples," but these are not examples of the instant method being used.

The examples in the specification which were used in the production of Figure 6 involved the isolation and sequencing of ESTs from fetal, normal, mild, and severe subjects with osteoarthritis. Example 1 teaches the extraction of RNA and cDNA library construction from fetal cartilage. The specification does not provide any details as to the number of individuals

whose cartilage is represented in the sample, and so the presumption is that the library represents the RNA of a single individual. A total of 13,398 sequences were obtained and sequenced from the library, of which 5,747 matched to known genes (specification p. 74). Example 2 teaches a similar extraction and sequencing of a cDNA library from "normal adult cartilage." Like in example 1, the specification does not provide any details as to the number of individuals whose cartilage is represented in the sample, and so, the presumption is that the library represents the RNA of a single individual. A total of 17,151 sequences were obtained and sequenced from the library, of which 6,755 matched to known genes (specification p. 75). Example 3 teaches a similar extraction and sequencing of a cDNA library from "mild osteoarthritic cartilage" and "severe osteoarthritic cartilage." Similar to the previous examples, the specification does not provide any details as to the number of individuals whose cartilage is represented in the samples, and so, the presumption is that the libraries represent the RNA of a single individual. A total of 12,651 and 14,222 sequences were obtained and sequenced from the mild and severe libraries, respectively, of which 43% and 51% matched to known genes (specification p. 77).

Example 4 states that genes that are differentially expressed between the libraries are identified through "relative EST frequency analysis," and the results are given in figure 6. Turning to figure 6, and referring specifically to the elected invention, data is given for each of the elected genes. The strongest relative differences were observed for beta-2-microglobulin gene (B2M). Expressed sequence tags (EST) from this gene represented 0.51% of the transcripts for normal, 1.58% for mild and 1.38% for severe OA samples. However, before reliable conclusions can be drawn in the diagnosis or staging of OA using just this gene or a group of genes comprising this gene as an indicator, there are many unresolved issues. First, given the

small sample size, it is not clear that these data are representative of any population or of simply of differences between individuals. No statistical analysis is given. For example, the relative expression is decreased in severe OA versus mild OA but it is increased in normal versus both of these. It is not clear from the specification what level of difference in expression is diagnostic of OA or a stage of OA. Further, the specification does not provide any controls of individuals with other diseases or disorders so that it is not clear if the differences in expression are specific to OA or are generalized responses to disease, for example. It is not clear that the test itself of "relative EST frequency" is valid given that the total pool of EST tested in each sample is different. The changes in "relative frequency" could be a result of differences in expression levels of other genes that cause the total number of expressed genes to increase or decrease relative to the gene in question. Almost every single gene that displayed appreciable expression in these libraries did so at different relative levels.

The data presented for the remaining genes in this group represents very low transcript numbers. A single MAFB EST was detected in fetal and normal samples, none in mild cases and 13 (representing 0.09%) in severe cases. Like B2M, there is not a progression from normal to severe in expression levels, instead, the mild case has no expression of this gene. It is not clear how to apply this result to diagnosis of any level of OA, alone or in combination with other genes, as claimed. The LAMC1 gene was detected only in fetal and normal cases with no expression in OA patients. Does this mean that the expression of LAMC1 in a patient is diagnostic of OA? The PF4 transcript was represented by a single EST in all three adult samples, thus there is no differential expression between normal and diseased samples since these all represent "0.01%" of the total sequenced EST. The IL13RA1 gene was represented in

OA patients but no in the fetal or control samples, but at such low levels it is not clear that this is indicative of any disease or if it is noise. Likewise, PER1 was represented in normal patients (one EST) but not in OA patients, but at such low levels in the normal patient it is not clear that this expression could be used for disease diagnosis. Zfr was not expressed in any adult sample. The specification does not address how such a result is used to diagnose disease. Likewise, CCNC was detected only in a single sequence in the mild OA library.

The some of the claims specifically recite detecting moderate or marked oseteoarthritis, but no data is given with regard to these stages. The claims are drawn to using a combination of genes for the diagnosis of OA or different stages of OA, yet the specification does not provide any guidance or discussion as to which expression patterns of the elected genes are diagnostic of disease or stages of the disease. The implication of the claims is that some diagnostic pattern of expression might be obtained by testing for the expression of the ten elected genes. However, the specification does not provide any guidance as to what this pattern is, how the expression of the different genes relates to the positive diagnosis of OA or any particular stage of OA as recited in the claims.

There is no guidance or evidence in the specification concerning differential expression in samples other than cartilage. The claims encompass the testing of a variety of samples, an specifically recite testing blood and synovial fluid in addition to cartilage.

Teachings in the Prior Art, Level of Unpredictability

It is highly unpredictable as to whether any of the apparent differential expression observed in applicant's experiments is specific to OA or to any stage of OA or if it represents some more generalized response which might be observed in a variety of different conditions.

For example, the B2M protein is a part of the class I MHC, and therefore would be expected to be expressed in a wide variety of circumstances in which the MHC is activated. For example, at the time the invention was made, differential expression of B2M had been observed in a variety of conditions. Riemer et al. observed increased expression of B2M in the brains of hamsters with the neurodegenerative disease scrapie, and teach that the activation of this gene (along with some additional genes) bears all of the hallmarks of a typical IFN response (Reimer et al. Journal of Virology, 2000, Vol. 74, No. 21, pages 10245-10248). At the time the invention was made, it was known that beta-2-microglobulin was produced in the synovial fluid of patients with rheumatoid arthritis at higher levels than from patients with non-RA diseases, including a patient with OA (Todesco et al., Journal of Rheumatology, 1980, 7(4)555-558, Table 1). Based on this finding, Todesco et al. suggest that B2M increases may have important diagnostic implications for rheumatoid arthritis (p. 557, 2nd column). Further, Babai et al. (US 5539096) teach that a clone smf-4, which corresponds to beta-2-microglobulin is over expressed in metastatic cell lines (Table 2, Col. 14, lines 31-35, and throughout).

The state of the art is highly unpredictable. It is impossible to predict, a priori, which gene transcript pattern would be diagnostic of OA, or even given data in the specification if there are any patterns that might be relevant for the ten elected genes and OA in general or for the different stages of OA. Particularly, in order to diagnose the different stages one would have to extrapolate from the data given what patterns might be used to indicate the presence of disease.

Quantity of Experimentation

The experimentation necessary to practice this invention would be enormous, if it were possible since this is such a highly unpredictable area. Given the data in the specification, one

would have to first undertake experimentation to confirm that in fact the genes in the elected group are differentially expressed in normal patients versus those with OA, and versus those patients having of the specifically recited stages of OA. Commensurate in scope with the claims, one would have to undertake this testing in a variety of tissues to confirm that any findings in cartilage would be equally applicable to additional tissues such as blood and synovial fluid. One would have to establish that the patterns of differential expression are specific to OA and stages of OA and not responses that would also be observed in other diseases such as rheumatoid arthritis and cancer, for example. All of this experimentation would have to be replicated in order to ensure that the relationships developed and the putative expression patterns are in fact sufficient to draw conclusions that OA or particular stages of OA are present, as recited in the claims.

Conclusion

Thus, given the unpredictability in this art area, given the lack of working examples and guidance in the specification, given the breadth of the claims and the nature of the invention, it is concluded that it would require undue experimentation in order to practice the claimed invention.

Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, W. Gary Jones can be reached by calling (571) 272-0745.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Primary Examiner
Art Unit 1634

May 26, 2005